End of Result Set

☐ Generate Collection

L6: Entry 2 of 2 File: USPT Dec 16, 1997

US-PAT-NO: 5698426
DOCUMENT-IDENTIFIER: US 5698426 A

TITLE: Surface expression libraries of heteromeric receptors

DATE-ISSUED: December 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

US-CL-CURRENT: 435/91.41; 435/320.1, 435/475, 435/69.1, 435/69.7, 530/387.1

ABSTRACT:

A composition of matter comprising a plurality of procaryotic cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form a heteromeric receptor exhibiting binding activity toward a preselected molecule, said heteromeric receptors being expressed on the surface of filamentous bacteriophage.

10 Claims, 16 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 16

End of Result Set

☐ Generate Collection

L1: Entry 34 of 34 File: USPT Nov 23, 1993

US-PAT-NO: 5264563
DOCUMENT-IDENTIFIER: US 5264563 A

TITLE: Process for synthesizing oligonucleotides with random codons

DATE-ISSUED: November 23, 1993

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Ixsys Inc.	San Diego	CA	N/A	N/A	02

APPL-NO: 7/ 990355
DATE FILED: December 14, 1992

PARENT-CASE:
This application is a continuation of application Ser. No. 07/573,648, filed Aug. 24, 1990, now abandoned.

INT-CL: [5] C07H 21/00, C07H 21/04

US-CL-ISSUED: 536/25.3; 536/25.31, 536/25.33, 536/25.34
US-CL-CURRENT: 536/25.3; 435/DIG.49, 536/25.31, 536/25.33, 536/25.34

FIELD-OF-SEARCH: 536/25.3, 536/25.31, 536/25.33, 536/25.34

REF-CITED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4458066	July 1984	Caruthers et al.	536/27
☐	4500707	February 1985	Caruthers et al.	536/25.3

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY
383620	August 1990	EPX

OTHER PUBLICATIONS

The Biochemistry of Nucleic Acids; 10th Edition (1986) Adams et al. pp. 11-12.
Fed. Proceedings vol. 42, No. 7 (1983) p. 2264 Blake et al.
Cwirla et al. Proc. Natl. Acad: Sci. vol. 87, pp. 6378-6382, 1990.
Devlin et al. Science, vol. 249, pp. 404-406, 1990.
Scott et al. Science, vol. 249, pp. 386-390, 1990.

ART-UNIT: 183

PRIMARY-EXAMINER: Rollins; John W.

ASSISTANT-EXAMINER: Kunz; Gary L.

ATTY, AGENT-FIRM: Campbell and Flores

ABSTRACT:

The invention provides a method of synthesizing oligonucleotides having random tuplets using individual monomers. The steps consist of: (1) sequentially coupling monomers on separate supports to form at least two different tuplets, the coupling is performed in separate reaction vessels; (2) mixing the supports from the reaction vessels; (3) dividing the mixed supports into two or more separate reaction vessels; and (4) repeating steps (1) through (3) one or more times in the reaction vessels of step (3), wherein the last step ends at step (2). Additionally, the oligonucleotides can be cleaved from the supports.

22 Claims, 2 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 2

BRIEF SUMMARY:

BACKGROUND OF THE INVENTION

This invention relates generally to oligonucleotide synthesis and, more particularly, to methods of synthesizing oligonucleotides having random codons using individual monomers.

The speed and availability of automated nucleic acid synthesis has led to rapid technological advances in biological research. For example, the availability of synthetic primers for sequencing has permitted researchers to decrease their time and labor involved in sequencing a particular nucleic acid by approximately sixty percent. Another technology which is facilitated by synthetic oligonucleotides is the polymerase chain reaction (PCR). This technique, which involves the exponential amplification of sequences between two synthetic primers, offers unprecedented detection levels and permits genetic manipulation of the amplified sequence. Further, the availability of synthetic primers allows a variety of genetic manipulations to be performed with relatively simple procedures, including site-specific mutagenesis and the custom design of genetic vectors.

Sequences to be cloned are also routinely modified with synthetic oligonucleotides. The modifications of either vector or insert sequence can range from the addition of a simple sequence encoding a restriction enzyme site to more complicated schemes involving modifying the translation product of the cloned sequence with a specific peptide or a variety of peptide sequences. Thus, these technological advances associated with synthetic oligonucleotides has afforded researchers many opportunities to study diverse biological phenomenon in greater detail and with greater speed and accuracy.

Oligonucleotide synthesis proceeds via linear coupling of individual monomers in a stepwise reaction. The reactions are generally performed on a solid phase support by first coupling the 3' end of the first monomer to the support. The second monomer is added to the 5' end of the first monomer in a condensation reaction to yield a dinucleotide coupled to the solid support. At the end of each coupling reaction, the by-products and unreacted, free monomers are washed away so that the starting material for the next round of synthesis is the pure oligonucleotide attached to the support. In this reaction scheme, the stepwise addition of individual monomers to a single, growing end of a oligonucleotide ensures accurate synthesis of the desired sequence. Moreover, unwanted side reactions are eliminated, such as the condensation of two. oligonucleotides, resulting in high product yields.

In some instances, it is desired that synthetic oligonucleotides have random nucleotide sequences. This result can be accomplished by adding equal proportions of all four nucleotides in the monomer coupling reactions, leading to the random incorporation of all nucleotides and yields a population of oligonucleotides with random sequences. Since all possible combinations of nucleotide sequences are represented within the population, all possible codon triplets will also be represented. If the objective is ultimately to generate random peptide products, this approach has a severe limitation because the random codons synthesized will bias the amino acids incorporated during translation of the DNA by the cell into polypeptides.

The bias is due to the redundancy of the genetic code. There are four nucleotide monomers which leads to sixty-four possible triplet codons. With only twenty amino acids to specify, many of the amino acids are encoded by multiple codons. Therefore, a population of oligonucleotides synthesized by sequential addition of monomers from a random population will not encode peptides whose amino acid sequence represents all possible combinations of the twenty different amino acids in equal proportions. That is, the frequency of amino acids incorporated into polypeptides will be biased toward those amino acids which are specified by multiple codons.

To alleviate amino acid bias due to the redundancy of the genetic code, the

End of Result Set

☐ Generate Collection

L2: Entry 2 of 2 File: USPT Nov 28, 1995

US-PAT-NO: 5470725
DOCUMENT-IDENTIFIER: US 5470725 A

TITLE: Thermostable (1,3-1,4)-.beta.-glucanase

DATE-ISSUED: November 28, 1995

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Borriss; Rainer	Berlin	N/A	N/A	DEX
Hofemeister; Jurgen	Gatersleben	N/A	N/A	DEX
Thomsen; Karl K.	Slagelse	N/A	N/A	DKX
Olsen; Ole	Copenhagen	N/A	N/A	DKX
Von Wettstein; Dietrich	V rlose	N/A	N/A	DKX

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Carlsberg A/S	Copenhagen	N/A	N/A	DKX	03
Akademie der Wissenchaften der DDR	Berlin	N/A	N/A	DEX	03

APPL-NO: 8/ 103998
DATE FILED: August 10, 1993

PARENT-CASE:
This application is a continuation of application Ser. No. 07/773,652, filed as PCT/DK90/00044, Feb. 16, 1990 now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
DD	325 8000	February 16, 1989
DK	3848/89	August 4, 1989

INT-CL: [6] C12P 19/02, C12N 9/24, C12N 15/56

US-CL-ISSUED: 435/93; 435/105, 435/200, 435/240.1, 435/243, 435/252.33, 435/254.21, 536/23.2
US-CL-CURRENT: 435/93; 435/105, 435/200, 435/243, 435/252.33, 435/254.21, 536/23.2

FIELD-OF-SEARCH: 435/200, 435/240.1, 435/243, 435/252.8, 435/93, 435/105, 435/252.33, 435/254.21, 536/23.2, 426/16, 426/52, 426/53

REF-CITED:

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY
0252666	January 1988	EPX
272102	September 1989	DEX

OTHER PUBLICATIONS

Politz, O., et al., (1993) Eur. J. Biochem 216, 829-834.
Argos et al. "Thermal Stability and Protein Structure", Biochemistry, 18:5698-5703 (1979).

Bolivar et al. "Construction and characterization of new cloning vehicle. II. A multipurpose cloning system," Gene 2:95-113 (1977).
Borriss "Purification and characterization of an extracellular beta-glucanase from

Bacillus IMET B376.sup.1)", Z. Alg. Mikrobiologie 21:507 (1981).
Borriss et al. ".beta.-1,3-1,4-glucanase in sporeforming microorganisms. V. The efficiency of .beta.-glucanase in reducing the viscosity of wort" Zbl. Bakt II Abt. 136:324-329 (1981).
Borriss et al. "Expression in Escherichia coli of a cloned .beta.-glucanase gene from Bacillus Amyloliquefaciens" Appl. Microbiol. Biotechnol. 22:63-71 (1985).
Borriss et al. "Molecular cloning of a gene coding for thermostable beta-glucanase from Bacillus macerans" J. Basic Microbiol. 28:3-10 (1988).
Bradford "A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein dye binding" Anal. Biochem. 72:248-254 (1976).
Cantwell et al. "Molecular cloning and expression of a Bacillus subtilis .beta.-glucanase gene in Escherichia coli" Gene 23:211-219 (1983).
Godfrey "On comparison of key characteristics of industrial enzymes by type and source," Industrial Enzymology, 5:466-569 (1983).
Hanahan "Techniques for transformation of E. coli" DNA Cloning, vol. 1, A practical approach., 6:109-135 (1985).
Hattori et al. "Dideoxy sequencing method using denatured plasmid templates" Anal. Chem. 152:232-238 (1986).
Hofemeister "The .beta.-glucanase gene from Bacillus amyloliquefaciens shows extensive homology with that of Bacillus subtilis" Gene 49:177-187 (1986).
Horton et al. "Engineering hybrid genes with the use of restriction enzymes: Gene splicing by overlap extension" Gene 77:61-68 (1989).
Imanaka et al. "A new way of enhancing the thermostability of proteases" Nature, 324:695-697 (1986).
Jorgensen "Quantification of high molecular weight (1-3 (1-4)-.beta.-D-glucan using calcofluor complex formation and flow injection analysis. I. Analytical principle and its standardization" Carlsberg Res. Commun. 53:277-285 (1988).
Jorgensen et al. "Quantification of high molecular weight (1-3)(1-4)-.beta.-D-glucan using calcofluor complex formation and flow injection analysis. II. Determination of total .beta.-glucan content of barley and malt," Carlsberg Res. Commun. 53 287-296 (1988).
Laemmli "Cleavage of structural proteins during the assembly of the head of bacteriophage T4" Nature 227:680-685 (1970).
Lederberg et al. "Transformation of Salmonella typhimurium by plasmid deoxyribonucleic acid" J. Bacteriol. 119:1072-1074 (1974).
Loi et al. "Survival of barley (1-3,1-4).beta.-D-glucanase isoenzymes during kilning and mashing" J. Cereal Sci. 5:45-50 (1987).
Matthews et al. "Enhanced protein thermostability from site-directed mutations that decrease the entropy of unfolding" Proc. Natl. Acad. Sci. 84:6663-6667 (1987).
McCleary "Soluble, dye-labeled polysaccharides for the assay of endohydrolases" Methods Enzymol. 160:74-86 (1988).
McFadden et al. "Expression sites and developmental regulation of genes encoding (1-3,1-4)-.beta.-D-glucanases in germinated barley" Planta 173:500-508 (1988).
Mead et al. "Single-stranded DNA `blue` T7 promoter plasmids: A versatile tandem promoter system for cloning and protein engineering" Protein Engineering 1:67-74 (1986).
Merrifield "Solid phase peptide synthesis. I. The synthesis of a tetrapetide" J. Am. Chem. Soc. 85:2149 (1963).
Miller "Use of dinitrosalicylic acid reagent for determination of reducing sugars" Analytical Chemistry 31:426-428 (1959).
Murphy "The DNA sequence of the gene and genetic control sites for the excreted B. subtilis enzyme .beta.-glucanase" Nucleic Acids Res. 12:5355-5367 (1984).
Querol "Tentative rules for increasing the thermostability of enzymes by protein engineering" Enzyme Microb. Technol. 9:238-244 (1987).
Shinnick et al. "Synthetic peptide immunogens as vaccines" Ann. Rev. Microbiol. 37:425-446 (1983).
Streuli et al. "Target cell specificity of two species of human interferon-alpha produced in Escherichia coli and of hybrid molecules derived from them" Prod. Natl. Acad. Sci. USA 78:2848-2852 (1981).
Thomsen "Mouse .alpha.-amylase synthesized by Saccharomyces cerevisiae is released into the culture medium" Carlsberg Res. Comm. 48:545-555 (1983).
Yanisch-Perron "Improved M13 phage cloning vectors and host strains: nucleotide sequences of the M13 mp18 and pUC19 vectors" Gene 33:103-119 (1985).
Weck et al. "Antiviral activities of hybrids of two major human leukocyte interferons" Nucleic Acids Res. 9:6153-6165 (1981).
Yon et al. "Precise gene fusion by PCR" Nucleic Acids Res. 17:4895 (1989).
Zhang et al. "Double stranded sequencing as a choice for DNA sequencing"Nucleic Acids Res. 16:1220 (1988).
Honda et al. "Cloning and expression in Escherichia coli of a Thermoanaerobacter cellulolyticus gene coding for heat-stable .beta.-glucanase" Appl Microbiol. Biotechnol. 25:480-483 (1987).
Petre et al. "Purification and properties of an endo-.beta.-1,4-glucanase from Clostridium thermocellum", (abst.) 7-Enzymes 95:145879q (1981), Biochemie 63:629-639 (1981).
Tikhomirov et al. "Endo-1,4-.beta.-glucanases of the anaerobic bacterium Clostridium thermocellum st. No. 3 with high heat stability" Chemical Abstracts 110:168879g (1989).
Schwarz et al. "Isolation of a Clostridium thermocellum gene encoding a thermostable .beta.-1,3-glucanase (laminarinase)" Chemical Abstracts 108:217067k (1988), Biotechnology Letters 10(4):225-230 (1988).

Kimosov et al. "A thermostable endo-1,4-beta.-glucanase from Myceliophthora thermophila" Chemical Abstracts 109:50624w (1988).

ART-UNIT: 184

PRIMARY-EXAMINER: Patterson, Jr.; Charles L.

ATTY-AGENT-FIRM: Foley & Lardner

ABSTRACT:

Novel hybrid thermostable (1,3-1,4)-.beta.-glucanases, their use in food manufacturing and feed manufacturing, DNA fragments encoding such glucanases, organisms expressing the DNA fragments and a method for producing the thermostable (1,3-1,4)-.beta.-glucanases. Hybrid fusion genes encoding Bacillus (1,3-1,4)-.beta.-glucanases were constructed, the gene products of which are more thermostable than any (1,3-1,4)-.beta.-glucanase known until now. The hybrid genes were constructed by reciprocal exchanges of the amino-terminal and carboxy-terminal parts of the .beta.-glucanase encoding genes from Bacillus amyloliquefaciens and Bacillus macerans. The resulting thermostable (1,3-1,4)-.beta.-glucanases retain a significant enzymatic activity at temperatures exceeding 65.degree. C. and at pH values below 5.0.

72 Claims, 15 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 15

BRIEF SUMMARY:

FIELD OF INVENTION

The present invention relates to novel thermostable (1,3-1,4)-.beta.-glucanases, the use of novel thermostable (1,3-1,4)-.beta.-glucanases, DNA fragments encoding such glucanases, organisms expressing the DNA fragments and a method for producing the thermostable (1,3-1,4)-.beta.-glucanases.

TECHNICAL BACKGROUND

(1,3-1,4)-.beta.-glucanases are used in the manufacture of different food products and animal feed and as subsidiary materials in biological research when it is necessary to cleave the .beta.-glycosidic linkages in (1,3-1,4)-.beta.-glucans. Especially in the brewing industry the use of such glucan hydrolyzing enzymes permits the application of larger proportions of raw grain in substitution for the use of malt, without this causing any trouble in the filtration due to high viscosity of the mash which may be caused by an increased amount of glucan compounds.

The mixed linked (1,3-1,4)-.beta.-glucans constitute the major part of the endosperm cell walls of cereals like oat and barley. They may cause severe problems in the brewing industry such as reduced yield of extract and lowered rates of wort separation or beer filtration. Remaining .beta.-glucans in the finished beer may lead to the formation of hazes and gelatinous precipitates (Godfrey, 1983). Barley (1,3-1,4)-.beta.-glucanases (EC 3.2.1.73) are synthesized in the scutellum and the aleurone layer during the early stages of germination of seeds (McFadden et al., 1988). However, a large proportion of the malt .beta.-glucanase is irreversibly heat inactivated during kilning and the remaining activity is rapidly destroyed during mashing (Loi et al., 1987).

It has long been known that the viscosity of the wort can be reduced by using .beta.-glucanases from mesophilic Bacillus strains, e.g. from Bacillus amyloliquefaciens or Bacillus subtilis. A serious disadvantage with the known glucanases is their temperature sensitivity, which implies that they are only effective during the early phase of the mashing process. Later on when temperatures are above 65.degree. C. their activity is reduced substantially.

In an attempt to obtain a more thermostable glucanase, the gene from Bacillus macerans encoding glucanase was introduced into Bacillus subtilis in order to express the gene in this organism (DD Patent Application WP C12N/315 706 1). However, at 70.degree. C. this glucanase is also rapidly and irreversibly denatured. Another drawback to the known glucanases in relation to the brewing process is that these glucanases do not exert their full activity in the pH range from 4 to 5 which is the normal condition during mashing. For example the activity of the Bacillus .beta.-glucanase at pH 4.6 is only 20% of that between 6 and 7. Furthermore, the stability is reduced when the glucanase is incubated at pH 4.

The best characterized bacterial (1,3-1,4)-.beta.-glucanases are those from Bacillus subtilis and B. amyloliquefaciens where the genes encoding the enzymes have been cloned

End of Result Set

☐ Generate Collection

L3: Entry 2 of 2 File: USPT Jun 4, 1996

US-PAT-NO: 5523388
DOCUMENT-IDENTIFIER: US 5523388 A

TITLE: Methods of synthesizing oligonucleotides with random codons

DATE-ISSUED: June 4, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Ixsys, Inc.	San Diego	CA	N/A	N/A	02

APPL-NO: 8/ 396346
DATE FILED: February 27, 1995

PARENT-CASE:
This application is a continuation of application Ser. No. 08/071,1473, filed on Jun. 4, 1993, which is abandoned, which is a continuation of application Ser. No. 07/990,355, filed on Dec. 14, 1992 (U.S. Pat. No. 5,264,563), which is a continuation of Ser. No. 07/573,648, filed on Aug. 24, 1990, which is abandoned.

INT-CL: [6] C07H 21/02, C07H 21/04

US-CL-ISSUED: 536/22.1; 536/25.3, 536/25.31, 536/25.33, 536/25.34
US-CL-CURRENT: 536/22.1; 536/25.3, 536/25.31, 536/25.33, 536/25.34

FIELD-OF-SEARCH: 536/22.1, 536/25.3, 536/25.31, 536/25.33, 536/25.34

REF-CITED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4458066	July 1984	Caruthers et al.	536/27
☐	4500707	February 1985	Caruthers et al.	536/25.3
☐	5082767	January 1992	Hatfield et al.	435/6
☐	5264563	November 1993	Huse	536/25.3

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY
383620	February 1990	EPX

OTHER PUBLICATIONS

Cwirla, Steven E. et al., "Peptides on phage: A Vast Library of Peptides for Identifying Ligands." Proc. Natl. Acad. Sci. USA. 87:6378-6382.
Devlin, James J. et al., "Random Peptide Libraries: A Source of Specific Protein Binding Molecules." Science 249:404-406 (1990).
Scott, Jamie K. and Smith, George P. "Searching for Peptide Ligands with an Epitope Library." Science 249:386-390 (1990).

Blake, R. D. et al. "Tuplet Analysis of Sequences." Federation Proceedings - Abstracts Indexes #2958. (1983).
Adams, Roger L. et al. The Biochemistry of the Nucleic Acids. Publisher: Chapman and Hall, London and New York. pp. 11-12 (1986).

ART-UNIT: 187

PRIMARY-EXAMINER: Jones; W. Gary

ASSISTANT-EXAMINER: Campbell; Eggerton

ATTY-AGENT-FIRM: Campbell and Flores

ABSTRACT:

The invention provides a method of synthesizing oligonucleotides having random tuplets using individual monomers. The steps consist of: (1) sequentially coupling monomers on separate supports to form at least two different tuplets, the coupling is performed in separate reaction vessels; (2) mixing the supports from the reaction vessels; (3) dividing the mixed supports into two or more separate reaction vessels; and (4) repeating steps (1) through (3) one or more times in the reaction vessels of step (3), wherein the last step ends at step (2). Additionally, the oligonucleotides can be cleaved from the supports.

20 Claims, 2 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 2

BRIEF SUMMARY:

BACKGROUND OF THE INVENTION

This invention relates generally to oligonucleotide synthesis and, more particularly, to methods of synthesizing oligonucleotides having random codons using individual monomers.

The speed and availability of automated nucleic acid synthesis has led to rapid technological advances in biological research. For example, the availability of synthetic primers for sequencing has permitted researchers to decrease their time and labor involved in sequencing a particular nucleic acid by approximately sixty percent. Another technology which is facilitated by synthetic oligonucleotides is the polymerase chain reaction (PCR). This technique, which involves the exponential amplification of sequences between two synthetic primers, offers unprecedented detection levels and permits genetic manipulation of the amplified sequence. Further, the availability of synthetic primers allows a variety of genetic manipulations to be performed with relatively simple procedures, including site-specific mutagenesis and the custom design of genetic vectors.

Sequences to be cloned are also routinely modified with synthetic oligonucleotides. The modifications of either vector or insert sequence can range from the addition of a simple sequence encoding a restriction enzyme site to more complicated schemes involving modifying the translation product of the cloned sequence with a specific peptide or a variety of peptide sequences. Thus, these technological advances associated with synthetic oligonucleotides has afforded researchers many opportunities to study diverse biological phenomenon in greater detail and with greater speed and accuracy.

Oligonucleotide synthesis proceeds via linear coupling of individual monomers in a stepwise reaction. The reactions are generally performed on a solid phase support by first coupling the 3' end of the first monomer to the support. The second monomer is added to the 5' end of the first monomer in a condensation reaction to yield a dinucleotide coupled to the solid support. At the end of each coupling reaction, the by-products and unreacted, free monomers are washed away so that the starting material for the next round of synthesis is the pure oligonucleotide attached to the support. In this reaction scheme, the stepwise addition of individual monomers to a single, growing end of a oligonucleotide ensures accurate synthesis of the desired sequence. Moreover, unwanted side reactions are eliminated, such as the condensation of two oligonucleotides, resulting in high product yields.

In some instances, it is desired that synthetic oligonucleotides have random nucleotide sequences. This result can be accomplished by adding equal proportions of all four nucleotides in the monomer coupling reactions, leading to the random incorporation of all nucleotides and yields a population of oligonucleotides with random sequences. Since all possible combinations of nucleotide sequences are represented within the population, all possible codon triplets will also be represented. If the objective is ultimately to generate random peptide products, this approach has a severe limitation because the random codons synthesized will bias the amino acids incorporated during translation of the DNA by the cell into polypeptides.

End of Result Set

☐ Generate Collection

L4: Entry 51 of 51 File: USPT Dec 31, 1996

US-PAT-NO: 5589466
DOCUMENT-IDENTIFIER: US 5589466 A

TITLE: Induction of a protective immune response in a mammal by injecting a DNA sequence

DATE-ISSUED: December 31, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Felgner; Philip L.	Rancho Santa Fe	CA	N/A	N/A
Wolff; Jon A.	Madison	WI	N/A	N/A
Rhodes; Gary H.	Leucadia	CA	N/A	N/A
Malone; Robert W.	Chicago	IL	N/A	N/A
Carson; Dennis A.	Del Mar	CA	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Vical Incorporated	San Diego	CA	N/A	N/A	02
Wisconsin Alumni Research Foundation	Dane	WI	N/A	N/A	02

APPL-NO: 8/ 380131
DATE FILED: January 26, 1995

PARENT-CASE:
This application is a continuation of application Ser. No. 08/008,197, filed Jan. 25, 1993, now abandoned, which is a continuation of application Ser. No. 07/496,991, filed Mar. 21, 1990, now abandoned, which is a continuation-in-part of application Ser. No. 467,881 filed Jan. 19, 1990, now abandoned which is a continuation-in-part of Ser. No. 326,305, filed Mar. 21, 1989, now abandoned.

INT-CL: [6] A61K 48/00, C12N 15/00

US-CL-ISSUED: 514/44; 935/53, 935/55, 935/60, 935/65
US-CL-CURRENT: 514/44; 424/184.1

FIELD-OF-SEARCH: 514/44, 935/53, 935/55, 935/60, 935/65

REF-CITED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	3931397	March 1976	Harnden	N/A
☐	4224404	April 1980	Viza et al.	N/A
☐	4394448	September 1983	Szoka	N/A
☐	4689320	February 1987	Kaji	N/A
☐	4699880	July 1987	Goldstein	N/A
☐	4704692	October 1987	Ladner	N/A
☐	4806463	November 1987	Goodchild	N/A
☐	4945050	July 1990	Sanford et al.	N/A

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY
188574	February 1986	EPX
0187702	July 1986	EPX
3102682	October 1988	JPX
1047381	February 1989	JPX
9001543	February 1990	WOX

OTHER PUBLICATIONS

Gal et al (1993) Lab. Invest. 68, 18-25.
Kitis et al (1991) Proced. Nat. Acad. Sci. 88, 4138-4142.
Buttrick et al (1992) Circul. Res. 70, 193-198.
Cox et al (1993) J. Virol. 67, 5664-5667.
Ulmer et al (1993) Science 259, 1745-1749.
Fynan et al (1993) Proced. Nat. Acad. Sci. 90, 11478-11482.
Wang et al (1993) Proced. Natl. Acad. Sci. 90, 4156-4160.
Yankauckas et al (1993) DNA and Cell Biol. 12, 771-776.
Hansen et al (1991) FEBS Letters 290, 73-76.
Jiao et al (1992) Human Gene Therapy 3, 21-33.
von Hardorf et al (1993) Circul. Res. 72, 688-659.
Ostro et al (1979) Nature 274, 921-923.
Magee et al (1978) Cancer Res. 38:1173-1176.
Fung, Y. K., et al., (1983) Tumor induction by direct injection of cloned v-src DNA into chickens. Proc. Natl. Acad. Sci. 80:353-357.
Yakubov, L., et al., (1989) Mechanism of oligonucleotide uptake by cells: involvement of specific receptors? Proc. Natl. Acad. Sci. 86:6454-6458.
Ausubel, Current Protocols in Mol. Biol., John Wiley & Sons, New York (1988) .sctn.1.5.2.2 .sctn..sctn. 9.1.1-9.1.4.
Adrian, et al. Mol. Cell. Biol. 4(9): 1712-1717 (1984).
Beardsley, et al. Scientific American 261(5): 28-30 (1989).
Been, et al. Cell 47: 206-216 (1986).
Benvenisty, et al. Proc. Natl. Acad. Sci. USA 83: 9551-9555.
Berge, et al. J. Pharm. Sciences 66: 1-19 (1977).
Brock, et al. Cell 34: 207-214 (1983).
Brown, et al. Science 232: 34-47 (1986).
Burmeister, et al. Cytogen. Cell. Genet. 46(1-4): 589 (1988).
de Wet, et al. Mol. Cell Biol. 7: 725-737 (1987).
Dean, et al. J. Cell. Biol. 106: 2159-2170 (1988).
Dolph, et al. J. of Virol. 62(6): 2059-2066 (1988).
Drummond, et al. Nucl. Acids Res. 13: 7375 (1985).
Dunn, et al. Gene 68: 259-266 (1988).
Eibl, et al. Biophys. Chem. 10: 261-271 (1979).
Elroy-Stein, et al. Proc. Natl. Acad. Sci. USA 86: 6126-6130.
Felgner, et al. Proc. Natl. Acad. Sci. USA 84: 7413-7417 (1987).
Felgner, et al. Proc. Natl. Acad. Sci. USA 84: 6730-6734 (1987).
Gillies, et al. Biotechnol. 7: 799-804 (1989).
Goodfellow, et al. Nature 341(6238): 102-103 (1989).
Graves, et al. Cell 48: 615-626 (1987).
Harland, et al. Development 102: 837-852 (1988).
Hentze, et al. Proc. Natl. Acad. Sci. USA 84: 6730-6734 (1987).
Hoffman, et al. Neuron 2: 1019-1029 (1989).
Holt, et al. Neuron 4: (1990).
Kabnick, et al. Mol. and Cell. Biol. 8: 3244-3250 (1988).
Kaneda, et al. Science 243: 375-378 (1989).
Klemenz, et al. EMBO Journal 4(8): 2053-2060 (1985).
Koenig, et al. Cell 53(2): 219-226 (1988).
Kozak, et al. Nucl. Acids Res. 15(20): 8125 (1987).
Kreig, et al. Nucl. Acids Res. 12(18): 7057-7070 (1984).
Malone, et al. Proc. Natl. Acad. Sci. USA 86: 6077-6081 (1989).
Mannino, et al. Biotechniques 6: 682-690 (1988).
McCrae, et al. Eur. J. of Biochem. 116: 467-470 (1981).
Mosier, et al. Nature 355: 256-259 (1988).
Muesing, et al. Cell 48: 691 (1987).
Mullner, et al. Cell 53: 815-825 (1988).
Nakatani, et al. Biotechnology 7: 805-810 (1989).
Namikawa, et al. Science 242: 1684-1686 (1988).
Nicolau, et al. Proc. Natl. Acad. Sci. USA 80: 1068-1072 (1983).
Norton, et al. Mol. Cell Biol. 5: 281-290 (1985).
Parks, et al. J. Virol. 60: 376-384 (1986).
Pelletier, et al. Nature 334: 320-325 (1988).

Posner, et al. Mol. Endocrinology 3(12): 1961-1968 (1989).
Rao, et al. Mol. and Cell. Biol. 8: 284 (1988).
Rommens, et al. Science 245(4922): 1059-1065 (1989).
Ross, et al. Mol. Biol. Med. 5: 1-14 (1988).
Selden, et al. Mol. Cell. Biol. 6: 3173-3179.
Shaw, et al. Cell 46: 659-667 (1986).
Stamatatos, et al. Biochemistry 27: 3917-3925 (1988).
Valerio, et al. Gene 31: 147-153 (1984).
Ward, et al. Nature 341: 544-546 (1989).
Watkins, et al. Nature 6176: 863-866 (1988).
Wickner, et al. Science 230: 400-407 (1985).
Ascadi, et al. The New Biologist 3(1): 71-81 (1991).
Hoffman, et al. Science 254: 1455-1456 (1991).
Lin, et al. Circulation 82: 2217-2221 (1990).
Price, et al. Proc. Natl. Acad. Sci. USA 84: 156-160 (1987).
Wu, et al. J. Biol. Chem. 263(29): 14621-14624 (1988).
Chen, et al. Mol. and Cell. Biol. 7: 2745-2752 (1987).
Dubensky, et al. Proc. Natl. Acad. Sci. USA 81: 5849-5852 (1984).
Friedman, et al. Science 244: 1275-1281 (1989).
Huang, et al. J. of Virol. 50: 417-424 (1984).
Loyter, et al. Exp. Cell Res. 139: 223-234 (1982).
Nicolau, et al. Methods in Enzymology 149: 157-176 (1987).
Straubinger, et al. Methods in Enzymology 101: 512-527 (1983).
Wu, et al. J. of Biol. Chem. 264: 16985-16987 (1989).
Bhoopalam, et al. Clin. Exp. Immunol. 23: 139-148 (1976).
Bouchard, et al. Virology 135: 53-64 (1984).
Wolff, et al. Nature, Jan. (1990).
Boynton, et al. Science 240: 1534-1538 (1988).
Daniell, et al. Proc. Natl. Acad. Sci. USA 87: 88-92 (1990).
Johnston, et al. Science 240: 1538-1541 (1988).
Brown, D., et al. (1988) Influence of env and long terminal repeat sequences on the tissue tropism of avian leukosis viruses. Journal of Virology 62(12):4828-4831.
Hentze, M., et al. (1987) A cis-acting element is necessary and sufficient for transnational regulation of human ferritin expression in response to iron. Proc. Natl. Acad. Sci. 84:6730-6734.
Holt, C., et al. (1990) Lipofection of cDNAs in the embryonic vertebrate central nervous system. Neuron 4:203-214.
Magee, W., et al. (1978) Marked stimulation of lymphocyte-mediated attack on tumor cells by target-directed liposomes containing immune RNA. Cancer Research 38:1173-1176.
New England Biolabs 1986/87 Catalog, 32 Tozer Rd., Beverly, MA 01915-0990 USA, p. 45.
Ostro, M., et al. (1978) Evidence for translation of rabbit globin mRNA after liposome-mediated insertion into a human cell line. Nature 274:921-923.
Robinson, H., et al. (1984) New findings on the congenital transmission of avian leukosis viruses. Science 225:417-419.
Selden, R., et al. (1988) Expression of the human growth hormone variant gene in cultured fibroblasts and transgenic mice. Proc. Natl. Acad. Sci. 85:8241-8245.
Wolff, J., et al. (1990) Direct gene transfer into mouse muscle in vivo. Science 23:1465-1468.
Chelly, J., et al., Transcription of the dystrophin gene in human muscle and non-muscle tissues, Nature 333:858-860 (1988).
Amato, I. "Tracing the Immune System's Evolutionary History" Science 261:164-165 (1993).
Merck World: 1-12 (Jul., 1993).
Agadjanyan, et al. Vaccines 94: 47-53 (1994).
Coney, et al. Vaccine 12(16): 1545-1550 (1994).
Davis, et al. Vaccine 12(16): 1503-1509 (1994).
Donnelly, et al. Vaccines 94: 55-59 (1994).
Haynes, et al. Vaccines 94: 65-70 (1994).
Hilleman, et al. The New York Academy, Abstr: Poster Presentation P4.
Hoffman, et al. Vaccine 12(16) 1529-1533.
Raz, et al. Proc. Natl. Acad. Sci. USA 91: 9519-9523 (1994).
Sedegah, et al. Proc. Natl. Acad. Sci. USA 91: 9866-9870 (1994).
Ulmer, et al. Vaccine 12(16): 1541-1544 (1994).
Wang, et al. Vaccines 94: 83-90 (1994).
Webster, et al. Vaccine 12(16): 1495-1498 (1994).
Xiang, et al. Virology 199: 132-140 (1994).
Xiang, et al. Immunity 2: 129-135 (1995).
Xu, et al. Vaccine 12(16): 1534-1536.
Zhou, et al. Vaccine 12(16): 1510-1514.

ART-UNIT: 184

PRIMARY-EXAMINER: Crouch; Deborah

ATTY-AGENT-FIRM: Knobbe, Martens, Olson & Bear

ABSTRACT:

A method for delivering an isolated polynucleotide such as DNA or RNA, to the interior of a cell in a mammal comprising the injection of an isolated polynucleotide into a muscle of the mammal where the polynucleotide is taken up by the cells of the muscle and exerts a therapeutic effect on the mammal. The method can be used to deliver a therapeutic polypeptide to the cells of the mammal, to provide an immune response upon in vivo translation of the polynucleotide, to deliver antisense polynucleotides, to deliver receptors to the cells of the mammal or to provide transitory gene therapy.

11 Claims, 10 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 9

BRIEF SUMMARY:

BACKGROUND OF THE INVENTION

The present invention relates to introduction of naked DNA and RNA sequences into a vertebrate to achieve controlled expression of a polypeptide. It is useful in gene therapy, vaccination, and any therapeutic situation in which a polypeptide should be administered to cells in vivo.

Current research in gene therapy has focused on "permanent" cures, in which DNA is integrated into the genome of the patient. Viral vectors are presently the most frequently used means for transforming the patient's cells and introducing DNA into the genome. In an indirect method, viral vectors, carrying new genetic information, are used to infect target cells removed from the body, and these cells are then re-implanted. Direct in vivo gene transfer into postnatal animals has been reported for formulations of DNA encapsulated in liposomes and DNA entrapped in proteoliposomes containing viral envelope receptor proteins (Nicolau et al., Proc. Natl. Acad Sci USA 80:1068-1072 (1983); Kaneda et al., Science 243:375-378 (1989); Mannino et al., Biotechniques 6:682-690 (1988). Positive results have also been described with calcium phosphate co-precipitated DNA (Benvenisty and Reshef Proc. Natl. Acad Sci USA 83:9551-9555 (1986)).

The clinical application of gene therapy, as well as the utilization of recombinant retrovirus vectors, has been delayed because of safety considerations. Integration of exogenous DNA into the genome of a cell can cause DNA damage and possible genetic changes in the recipient cell that could predispose to malignancy. A method which avoids these potential problems would be of significant benefit in making gene therapy safe and effective.

Vaccination with immunogenic proteins has eliminated or reduced the incidence of many diseases; however there are major difficulties in using proteins associated with other pathogens and disease states as immunogens. Many protein antigens are not intrinsically immunogenic. More often, they are not effective as vaccines because of the manner in which the immune system operates.

The immune system of vertebrates consists of several interacting components. The best characterized and most important parts are the humoral and cellular (cytolytic) branches. Humoral immunity involves antibodies, proteins which are secreted into the body fluids and which directly recognize an antigen. The cellular system, in contrast, relies on special cells which recognize and kill other cells which are producing foreign antigens. This basic functional division reflects two different strategies of immune defense. Humoral immunity is mainly directed at antigens which are exogenous to the animal whereas the cellular system responds to antigens which are actively synthesized within the animal.

Antibody molecules, the effectors of humoral immunity, are secreted by special B lymphoid cells, B cells, in response to antigen. Antibodies can bind to and inactivate antigen directly (neutralizing antibodies) or activate other cells of the immune system to destroy the antigen.

Cellular immune recognition is mediated by a special class of lymphoid cells, the cytotoxic T cells. These cells do not recognize whole antigens but instead they respond to degraded peptide fragments thereof which appear on the surface of the target cell bound to proteins called class I major histocompatibility complex (MHC) molecules. Essentially all nucleated cells have class I molecules. It is believed that proteins produced within the cell are continually degraded to peptides as part of normal cellular metabolism. These fragments are bound to the MHC molecules and are transported to the cell surface. Thus the cellular immune system is constantly monitoring the spectra of proteins produced in all cells in the body and is poised to eliminate any cells producing foreign antigens.

Vaccination is the process of preparing an animal to respond to an antigen. Vaccination is more complex than immune recognition and involves not only B cells and cytotoxic T cells but other types of lymphoid cells as well. During vaccination, cells which recognize the

End of Result Set

☐ Generate Collection

L5: Entry 19 of 19 File: USPT Jan 14, 1997

US-PAT-NO: 5593972
DOCUMENT-IDENTIFIER: US 5593972 A

TITLE: Genetic immunization

DATE-ISSUED: January 14, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Weiner; David B.	Merion	PA	N/A	N/A
Williams; William V.	Havertown	PA	N/A	N/A
Wang; Bin	Havertown	PA	N/A	N/A

ASSIGNEE INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Wistar Institute	Philadelphia	PA	N/A	N/A	02
The Trustees of the University of Pennsylvania	Philadelphia	PA	N/A	N/A	02

APPL-NO: 8/ 125012
DATE FILED: September 21, 1993

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a Continuation-In-Part application of U.S. patent application Ser. No. 08/029,336 filed Mar. 11, 1993, now abandoned; which is a Continuation-In-Part application of U.S. patent application Ser. No. 08/008,342 filed Jan. 26, 1993, abandoned; both of which are incorporated herein by reference.

INT-CL: [6] A61K 45/05, A61K 48/00, A61K 31/00

US-CL-ISSUED: 514/44; 424/278.1, 514/615, 514/818
US-CL-CURRENT: 514/44; 424/278.1, 514/615, 514/818

FIELD-OF-SEARCH: 435/320.1, 424/93.1, 424/93.2, 424/93.21, 424/278.1, 514/44, 514/615, 514/818

REF-CITED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4224404	September 1980	Viza et al.	435/2
☐	4394448	July 1983	Szoka, Jr. et al.	435/172.3
☐	4806463	February 1989	Goodchild et al.	435/5
☐	4945050	July 1990	Sanford et al.	435/172.1
☐	5017487	May 1991	Stunnenberg et al.	435/172.3
☐	5036006	July 1991	Sanford et al.	435/170.1
☐	5185254	February 1993	Linnenbach	435/172.3
☐	5466676	November 1995	Booth et al.	514/44

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY
WO90/11092	October 1990	WOX
WO91/12329	August 1991	WOX
WO93/17706	September 1993	WOX
WO93/23552	November 1993	WOX

OTHER PUBLICATIONS

F. D. Ledley (1991) Human Gene Therapy 2:77-83.
B. F. Haynes (1993) Science 260: 1279-1286.
A. Hoffenbach et al. (1989) The Journal of Immunology 142: 452-462.
D. Torpey et al. (1993) Clinical Immunology and Immunopathology 68(3): 263-272.
L. Butini et al. (1994) J. Cell. Biochem. Suppl. 18B: 147, Abstract J306.
A. Knuth et al (1991) Current Opinion in Immunology 3:659-664.
B. Wang et al (1993) Proc. Natl. Acad. Sci. USA 90:4156-4160.
D. J. Wells (1993) Febs Letters 332 (1,2):179-182.
R. F. Garry et al. (1990) Science 250: 1127-1129.
A. M. Schultz et al., AIDS 7(suppl. 1):S161-S170 (1993).
V. Glaser, Genetic Engineering News 16(1):6 (1996).
H. N. Eisen, "Introduction to Immune Responses," in Microbiology, Bernard D. Davis et al., eds. Hagerstown: Harper & Row, Publishers, 1980, p. 294.
Aldovini et al., "Mutations of RNA and Protein Sequences Involved in Human Immunodeficiency Virus Type 1 Packaging Result in Production of Noninfectious Virus," J. of Virology, 64: 1920-1926, 1990.
Benvenisty et al., "Direct introduction of genes into rats and expression of the genes," Proc. Natl. Acad. Sci. USA, 83:9551-9555, 1986.
Brandsma et al., "Use of a rapid, efficient inoculation method to induce papillomas by conttontail rabbit papillomavirus DNA shows that the E7 gene is required," Proc. Natl. Acad. Sci. USA, 88:4816-4820, 1991.
Desrosiers, "HIV with Multiple Gene Deletions as a Live Attenuated Vaccine for AIDS," AIDS Research and Human Retroviruses, 8:411-421, 1992.
Friedmann et al., "Progress Toward Human Gene Therapy," Science, 244:1275-1281, 1989.
Kaneda et al., "Increased Expression of DNA Cointroduced with Nuclear Protein in Adult Rat Liver," Science, 243:375-378, 1989.
Nicolau et al., "In vivo expression of rat insulin after intravenous administration of the liposome-entrapped gene for rat insulin I," Proc. Natl. Acad. Sci. USA, 80:1068-1072, 1983.
Ronen et al., "Expession of wild-type and mutant p53 proteins by recombinant vaccinia viruses," Nucleic Acids Research, 20:3435-3441, 1992.
Schauer et al., "The N-Terminal Region of HIV-1 Integrase is Required for Integration Activity, but not for DNA-Binding," Biochem. and Biophys. Res. Commun., 185:874-880, 1992.

Seeger et al., "The cloned genome of ground squirrel hepatitis virus is infectious in the animal," Proc. Natl. Acad. Sci. USA, 81:5849-5852, 1984.
Wu et al., "Receptor-mediated Gene Delivery and expression in Vivo," J. of Biological Chemistry, 263:14621-14624, 1988.
Yang et al., "In vivo and in vitro gene transfer to mammalian somatic cells by particle bombardment," Proc. Natl. Acad. Sci. USA, 87:9568-9572, 1990.
Zelenin et al., "High-velocity mechanical DNA transfer of the chloramphenicolacetyl transferase gene into rodent liver, kidney and mammary gland cells in organ explants and in vivo," FEBS Letts., 280:94-96, 1991.
Acsadi et al., "Human dystrophin expression in mdx mice after intramuscular injection of DNA constructs," Nature 352:815-818, 1991.
Anderson, W. French, "Prospects for Human Gene Therapy," Science 226:401-409, 1984.
Anilionis et al., "Structure of the glycoprotein gene in rabies virus," Nature 294:275278, 1981.
Benoit et al., "Destruction and regeneration of skeletal muscle after treatment with a local anaesthetic, bupivacaine (Marcaine.RTM.)," J. Anat. 107:547-556, 1970.
Berman et al., "Protection of chimpanzees from infection by HIV-1 after vaccination with recombinant glycoprotein gp120 but not gp160," Nature, 345:622-625, 1990.
Brigham et al., "Rapid Communication: In Vivo Transfection of Murine Lungs with a Functioning Prokaryotic Gene Using A Liposome Vehicle," American Journal of the Medical Sciences, 298:278-281, 1989.
Chaudhary et al., "A rapid method of cloning functional variable-region antibody genes in Escherichia coli as single-chain immunotoxins," Proc. Natl. Acad. Sci. USA, 87:1066-1070, 1990.
Chen et al., "HIV-1 gp41 contains two sites for interaction with several proteins on the helper T-lymphoid cell line, H9," AIDS, 6:533-539, 1992.
Cheng-Mayer et al., "Human Immunodeficiency virus can productively infect cultured human glial cells," Proc. Natl. Acad. Sci. USA, 84:3526-3530, 1987.
Crowe et al., "Improved cloning efficiency of polymerase chain reaction (PCR) products after proteinase K digestion", Nucleic Acids Research, 19:184, 1991.

Desquenne-Clark et al., "T-cell receptor peptide immunization leads to enhanced and chronic experimental allergic encephalomyelitis," Proc. Natl. Acad. Sci. USA, 88:7219-7223, 1991.
Di Fiore et al., "erbB-2 Is a Potent Oncogene When Overexpressed in NIH/3T3 Cells," Science, 237:178-182, 1987.
Dubensky et al., "Direct transfection of viral and plasmid DNA into the liver of spleen of mice," Proc. Natl. Acad. Sci. USA, 81:7529-7533, 1984.
Felgner et al., "Gene Therapeutics," Nature, 349:351-352, 1991.
Fisher et al., "A molecular clone of HTLV-III with biological activity," Nature, 316:262-265, 1985.
Fisher et al., "HIV infection is blocked in vitro by recombinant soluble CD4," Nature, 331:76-78, 1988.
Goudsmit et al., "Human antibody response to a strain-specific HIV-1 gp120 epitope associated with cell fusion inhibition," AIDS, 2:157-164, 1988.
Hahn et al., "Suppression of Murine Lupus Nephritis By Administration of an Anti-Idiotypic Antibody to Anti-DNA," J. of Immunology, 132:187-190, 1984.
Hall-Craggs, E. C. B., "Rapid Degeneration and Regeneration of a Whole Skeletal Muscle Following Treatment with Bupivacain (Marcain)," Experimental Neurology, 43:349-358, 1974.
Howley, Peter M., "Papillomavirinae and Their Replication," Virology, Chapter 58:1625-1650, 1990.
Howell et al., "Limited T-cell receptor Beta-chain heterogeneity among interleukin 2 receptor-positive synovial T cells suggests a role for superantigen in rheumatoid arthritis," Proc. Natl. Acad. Sci. USA, 88:10921-10925, 1991.
Israel et al., "Biological Activity of Polyoma Viral DNA in Mice and Hamsters," J. of Virology, 29:990-996, 1979.
Klein et al., "Transformation of Microbes, Plants and Animals by Particle Bombardment," Bio/Technology, 10:286-291, 1992.
Koenig et al., "Detection of AIDS Virus in Macrophages in Brian Tissue from AIDS Patients with Encephalopathy," Science, 233:1089-1093, 1986.
Kowalski et al., "Functional Regions of the Envelope Glycoprotein of Human Immunodeficiency Virus Type 1," Science, 237:1351-1355, 1987.
Langlois et al., "The Ability of Certain HIV Vaccines to Provoke Reactions Against Normal Cells," Science, 255:292-293, 1992.
Lasky et al., "Neutralization of the AIDS Retrovirus by Antibodies to a Recombinant Envelope Glycoprotein," Science, 233:209-212, 1986.
Lasky et al., "Delineation of a Region of the Human Immunodeficiency Virus Type 1 gp120 Glycoprotein Critical for Interaction with the CD4 Receptor," Cell, 50:975-985, 1987.
Letvin et al., "Risks of Handling HIV," Nature, 349:573, 1991.
Maddon et al., "The T4 Gene Encodes the AIDS Virus Receptor and Is Expressed in the Immune System and the Brain," Cell, 47:333-348, 1986.
Montefiori et al., "Evaluation of Antiviral Drugs and Neutralizing Antibodies to Human Immunodeficiency Virus by a Rapid and Sensitive Microtiter Infection Assay," J. of Clinical Microbiology, 26:231-235, 1988.
Morgenstern et al., "Advanced mammalian gene transfer: high titre retroviral vectors with multiple drug selection markers and a complementary helper-free packaging cell line," Nucl. Acids Res., 18:3587-3596, 1990.
Nabel et al., "Site-Specific Gene Expression in Vivo by Direct Gene Transfer into the Arterial Wall," Science, 249:1285-1288, 1990.
Nara, Peter L., "Quantitative Infectivity Syncytium-Forming Microassay," Basic Virologic Techniques, 77-86.
Oksenberg et al., "Limited heterogeneity of rearranged T-cell receptor V alpha transcripts in brains of multiple sclerosis patients," Nature, 345:344-348, 1990.
Osther et al., "Protective Humoral Immune Responses to the Human Immunodeficiency Virus Induced in Immunized Pigs: A Possible Source of Therapeutic Immunoglobulin Preparations," Hybridoma, 10:673-683, 1991.
Osther et al., "The Quick Western Blot, A Novel Transportable 50-Minute HIV-1 Antibody Test," Transplantation, 47:834-838, 1989.
Paliard et al., "Evidence for the Effects of a Superantigen in Rheumatoid Arthritis," Science, 253:325-329, 1991.
Putney et al., "Development of an HIV Subunit Vaccine," V International Conference on AIDS, Quebec, Canada; Jun. 4-9, 1989.
Schrier et al., "B-and T-Lymphocyte Responses to an Immunodominant Epitope of Human Immunodeficiency Virus," J. of Virology, 62:2531-2536, 1988.
Sun et al., "Generation and Characterization of Monoclonal Antibodies to the Putative CD4-Binding Domain of Human Immunodeficiency Virus Type 1 gp120," J. of Virology, 63:3579-3585, 1989.
Shah et al., "Papillomaviruses," Virology, Chapter 59:1651-1676, 1990.
Seed et al., "Molecular cloning of the CD2 antigen, the T-cell erythrocyte receptor, by a rapid immunoselection procedure," Proc. Natl. Acad. Sci. USA, 84:3365-3369, 1987.
Szala et al., "Molecular cloning of cDNA for the carcinoma-associated antigen GA733-2," Proc. Natl. Acad. Sci. USA, 87:3542-3546, 1990.
Tang et al., "Genetic immunization is a simple method for eliciting an immune response", Nature 356:152-154, 1992.
Teitelbaum et al., "In Vivo Effects of Antibodies Against a High Frequency Idiotype of Anti-DNA Antibodies in MRL Mice," 132:1282-1285, 1984.
Thomason et al., "Stable incorporation of a bacterial gene into adult rat skeletal muscle

End of Result Set

☐ Generate Collection

L6: Entry 2 of 2 File: USPT Dec 16, 1997

US-PAT-NO: 5698426
DOCUMENT-IDENTIFIER: US 5698426 A

TITLE: Surface expression libraries of heteromeric receptors

DATE-ISSUED: December 16, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

US-CL-CURRENT: 435/91.41; 435/320.1, 435/475, 435/69.1, 435/69.7, 530/387.1

ABSTRACT:

A composition of matter comprising a plurality of procaryotic cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form a heteromeric receptor exhibiting binding activity toward a preselected molecule, said heteromeric receptors being expressed on the surface of filamentous bacteriophage.

10 Claims, 16 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 16

End of Result Set

☐ Generate Collection

L7: Entry 2 of 2 File: USPT Dec 30, 1997

US-PAT-NO: 5703057
DOCUMENT-IDENTIFIER: US 5703057 A

TITLE: Expression library immunization

DATE-ISSUED: December 30, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnston; Stephen A.	Dallas	TX	N/A	N/A
Barry; Michael A.	Carrollton	TX	N/A	N/A
Lai; Wayne C.	Richardson	TX	N/A	N/A

US-CL-CURRENT: 514/44; 424/422, 424/423, 424/9.2, 435/320.1, 435/325, 435/6, 435/7.1, 536/22.1, 536/23.1, 536/23.2, 536/23.4, 536/23.5, 536/23.51, 536/23.7, 536/23.72, 536/23.74

ABSTRACT:

A general method for vaccinating against any pathogen is presented. The method utilizes expression library immunization, where an animal is inoculated with an expression library constructed from fragmented genomic DNA of the pathogen. All potential epitopes of the pathogen's proteins are encoded in its DNA, and genetic immunization is used to directly introduce one or more expression library clones to the immune system, producing an immune response to the encoded protein. Inoculation of expression libraries representing portions of the Mycoplasma pulmonis genome was shown to protect mice from subsequent challenge by this natural pathogen. Protection against Listeria was also obtained using the method.

30 Claims, 14 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 12

End of Result Set

☐ Generate Collection

L8: Entry 12 of 12 File: USPT Mar 3, 1998

US-PAT-NO: 5723323
DOCUMENT-IDENTIFIER: US 5723323 A

TITLE: Method of identifying a stochastically-generated peptide, polypeptide, or protein having ligand binding property and compositions thereof

DATE-ISSUED: March 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kauffman; Stuart Alan	Santa Fe	NM	87501	N/A
Ballivet; Marc	1028 Geneva	N/A	N/A	CHX

US-CL-CURRENT: 435/6; 435/69.1, 435/7.1, 435/91.1, 530/300, 530/350, 536/23.1

ABSTRACT:

The present invention is directed to a process for the production of a peptide, polypeptide, or protein having a predetermined property. In accordance with one embodiment, the process begins by producing by way of synthetic polynucleotide coupling, stochastically generated polynucleotide sequences. A library of expression vectors containing such stochastically generated polynucleotide sequences is formed. Next, host cells containing the vectors are cultured so as to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences. Screening or selection is carried out on such host cells to identify a peptide, polypeptide, or protein produced by the host cells which has the predetermined property. The stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein is then isolated and used to produce the peptide, polypeptide, or protein having the predetermined property.

48 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

☐ Generate Collection

L9: Entry 2 of 2 File: USPT Jun 9, 1998

US-PAT-NO: 5763192
DOCUMENT-IDENTIFIER: US 5763192 A

TITLE: Process for obtaining DNA, RNA, peptides, polypeptides, or protein, by recombinant DNA technique

DATE-ISSUED: June 9, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kauffman; Stuart Alan	Bryn Mawr	PA	N/A	N/A
Ballivet; Marc	Geneva	N/A	N/A	CHX

US-CL-CURRENT: 435/7.1; 435/69.1, 435/91.1, 536/23.1

ABSTRACT:

The present invention is directed to a process for the production of a peptide, polypeptide, or protein having a predetermined property. In accordance with one embodiment, the process begins by producing by way of synthetic polynucleotide coupling, stochastically generated polynucleotide sequences. A library of expression vectors containing such stochastically generated polynucleotide sequences is formed. Next, host cells containing the vectors are cultured so as to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences. Screening or selection is carried out on such host cells to identify a peptide, polypeptide, or protein produced by the host cells which has the predetermined property. The stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein is then isolated and used to produce the peptide, polypeptide, or protein having the predetermined property.

5 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

☐ Generate Collection

L10: Entry 2 of 2 File: USPT Jun 23, 1998

US-PAT-NO: 5770434
DOCUMENT-IDENTIFIER: US 5770434 A

TITLE: Soluble peptides having constrained, secondary conformation in solution and method of making same

DATE-ISSUED: June 23, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

US-CL-CURRENT: 435/252.33; 435/320.1

ABSTRACT:

A method of synthesizing isolated, soluble peptides having constrained secondary structure in solution is described herein. The peptides are encoded by expressible oligonucleotides having a desirable bias of random codon sequences.

37 Claims, 28 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 28

End of Result Set

☐ Generate Collection

L12: Entry 1 of 1 File: USPT Jul 21, 1998

US-PAT-NO: 5783386
DOCUMENT-IDENTIFIER: US 5783386 A

TITLE: Mycobacteria virulence factors and a novel method for their identification

DATE-ISSUED: July 21, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Jacobs, Jr.; William R.	City Island	NY	N/A	N/A
Bloom; Barry R.	Hastings-on-Hudson	NY	N/A	N/A
Collins; Desmond Michael	Wellington	N/A	N/A	NZX
de Lisle; Geoffrey W.	Wellington	N/A	N/A	NZX
Pascopella; Lisa	Hamilton	MT	N/A	N/A
Kawakami; Riku Pamela	Wellington	N/A	N/A	NZX

US-CL-CURRENT: 435/6; 424/248.1, 435/91.2

ABSTRACT:

Polynucleotides associated with virulence in mycobacteria, and particularly a fragment of DNA isolated from M. bovis that contains a region encoding a putative sigma factor. Also provided are methods for a DNA sequence or sequences associated with virulence determinants in mycobacteria, and particularly in M. tuberculosis and M. bovis. The invention also provides corresponding polynucleotides associated with avirulence in mycobacteria. In addition, the invention provides a method for producing strains with altered virulence or other properties which can themselves be used to identify and manipulate individual genes.

3 Claims, 34 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 32

End of Result Set

☐ Generate Collection

L13: Entry 1 of 1 File: USPT Sep 15, 1998

US-PAT-NO: 5808022
DOCUMENT-IDENTIFIER: US 5808022 A

TITLE: Oligonucleotides having random riplets

DATE-ISSUED: September 15, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

US-CL-CURRENT: 536/22.1; 536/23.1

ABSTRACT:

The invention provides a method of synthesizing oligonucleotides having random tuplets using individual monomers. The steps consist of: (1) sequentially coupling monomers on separate supports to form at least two different tuplets, the coupling is performed in separate reaction vessels; (2) mixing the supports from the reaction vessels; (3) dividing the mixed supports into two or more separate reaction vessels; and (4) repeating steps (1) through (3) one or more times in the reaction vessels of step (3), wherein the last step ends at step (2). Additionally, the oligonucleotides can be cleaved from the supports.

4 Claims, 2 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 2

End of Result Set

☐ Generate Collection

L14: Entry 2 of 2 File: USPT Sep 29, 1998

US-PAT-NO: 5814476
DOCUMENT-IDENTIFIER: US 5814476 A

TITLE: Process for the production of stochastically-generated transcription or translation products

DATE-ISSUED: September 29, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kauffman; Stuart Alan	Bryn Mawr	PA	N/A	N/A
Ballivet; Marc	Geneva	N/A	N/A	CHX

US-CL-CURRENT: 435/69.1; 435/320.1, 435/6, 435/7.1, 435/91.1, 530/300, 530/350, 536/23.1

ABSTRACT:

The present invention is directed to a process for the production of a peptide, polypeptide, or protein having a predetermined property. In accordance with one embodiment, the process begins by producing by way of synthetic polynucleotide coupling, stochastically generated polynucleotide sequences. A library of expression vectors containing such stochastically generated polynucleotide sequences is formed. Next, host cells containing the vectors are cultured so as to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences. Screening or selection is carried out on such host cells to identify a peptide, polypeptide, or protein produced by the host cells which has the predetermined property. The stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein is then isolated and used to produce the peptide, polypeptide, or protein having the predetermined property.

107 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

Generate Collection

L15: Entry 2 of 2 File: USPT Oct 6, 1998

US-PAT-NO: 5817483
DOCUMENT-IDENTIFIER: US 5817483 A

TITLE: Process for the production of stochastically-generated peptides,polypeptides or proteins having a predetermined property

DATE-ISSUED: October 6, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kauffman; Stuart Alan	Bryn Mawr	PA	N/A	N/A
Ballivet; Marc	Geneva	N/A	N/A	CHX

US-CL-CURRENT: 435/69.1; 435/320.1, 435/7.1, 435/91.1, 530/300, 530/350, 536/23.1

ABSTRACT:

The present invention is directed to a process for the production of a peptide, polypeptide, or protein having a predetermined property. In accordance with one embodiment, the process begins by producing by way of synthetic polynucleotide coupling, stochastically generated polynucleotide sequences. A library of expression vectors containing such stochastically generated polynucleotide sequences is formed. Next, host cells containing the vectors are cultured so as to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences. Screening or selection is carried out on such host cells to identify a peptide, polypeptide, or protein produced by the host cells which has the predetermined property. The stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein is then isolated and used to produce the peptide, polypeptide, or protein having the predetermined property.

53 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

☐ Generate Collection

L16: Entry 1 of 1 File: USPT Oct 20, 1998

US-PAT-NO: 5824469
DOCUMENT-IDENTIFIER: US 5824469 A

TITLE: Method for producing novel DNA sequences with biological activity

DATE-ISSUED: October 20, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Horwitz; Marshall S.	Bellevue	WA	N/A	N/A
Loeb; Lawrence A.	Bellevue	WA	N/A	N/A

US-CL-CURRENT: 435/6; 435/488, 435/91.1, 536/23.1, 536/24.1

ABSTRACT:

A method of obtaining an oligonucleotide capable of carrying out a predetermined biological function. A heterogeneous pool of oligonucleotides, x+y+z nucleotides in length, is first generated. Each oligonucleotide has a 5' randomized sequence, x nucleotides in length, a central preselected sequence, y nucleotides in length, and a 3' randomized sequence, z nucleotides in length. The resulting heterogeneous pool contains nucleic acid sequences representing a random sampling of the 4.sup.x+z possible sequences for oligonucleotides of the stated length. A random sampling of the heterogeneous pool of oligonucleotides is introduced into a population of cells that do not exhibit the predetermined biological function. The population of engineered cells is then screened for a subpopulation of cells exhibiting the predetermined biological function. From that subpopulation of cells is isolated an oligonucleotide containing the preselected sequence and capable of carrying out the predetermined biological function.

3 Claims, 7 Drawing figures Exemplary Claim Number: 3
Number of Drawing Sheets: 7

End of Result Set

☐ Generate Collection

L17: Entry 2 of 2 File: USPT Oct 20, 1998

US-PAT-NO: 5824514
DOCUMENT-IDENTIFIER: US 5824514 A

TITLE: Process for the production of expression vectors comprising at least one stochastic sequence of polynucleotides

DATE-ISSUED: October 20, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kauffman; Stuart Alan	Santa Fe	NM	N/A	N/A
Ballivet; Marc	Geneva	N/A	N/A	CHX

US-CL-CURRENT: 435/91.1; 435/320.1, 435/488, 435/489, 435/69.1, 536/23.1

ABSTRACT:

The present invention is directed to a process for the production of a peptide, polypeptide, or protein having a predetermined property. In accordance with one embodiment, the process begins by producing by way of synthetic polynucleotide coupling, stochastically generated polynucleotide sequences. A library of expression vectors containing such stochastically generated polynucleotide sequences is formed. Next, host cells containing the vectors are cultured so as to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences. Screening or selection is carried out on such host cells to identify a peptide, polypeptide, or protein produced by the host cells which has the predetermined property. The stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein is then isolated and used to produce the peptide, polypeptide, or protein having the predetermined property.

46 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

☐ Generate Collection

L18: Entry 1 of 1 File: USPT Nov 3, 1998

US-PAT-NO: 5830696
DOCUMENT-IDENTIFIER: US 5830696 A

TITLE: Directed evolution of thermophilic enzymes

DATE-ISSUED: November 3, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A

US-CL-CURRENT: 435/69.1; 530/350

ABSTRACT:

Thermostable enzyme are subjected to mutagenesis to produce a thermophilic enzyme which is stable at thermophilic temperature and which has increased activities at least two-fold higher than the activity of the wild-type thermostable enzyme at lower temperatures, which are temperatures of 50.degree. C. or lower.

2 Claims, 3 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 3

End of Result Set

☐ Generate Collection

L19: Entry 6 of 6 File: USPT Nov 17, 1998

US-PAT-NO: 5837458
DOCUMENT-IDENTIFIER: US 5837458 A

TITLE: Methods and compositions for cellular and metabolic engineering

DATE-ISSUED: November 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Minshull; Jeremy	San Francisco	CA	N/A	N/A
Stemmer; Willem P. C.	Los Gatos	CA	N/A	N/A

US-CL-CURRENT: 435/6

ABSTRACT:

The present invention is generally directed to the evolution of new metabolic pathways and the enhancement of bioprocessing through a process herein termed recursive sequence recombination. Recursive sequence recombination entails performing iterative cycles of recombination and screening or selection to "evolve" individual genes, whole plasmids or viruses, multigene clusters, or even whole genomes. Such techniques do not require the extensive analysis and computation required by conventional methods for metabolic engineering.

36 Claims, 1 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 1

End of Result Set

Generate Collection

L20: Entry 1 of 1 File: USPT Feb 2, 1999

US-PAT-NO: 5866363
DOCUMENT-IDENTIFIER: US 5866363 A

TITLE: Method and means for sorting and identifying biological information

DATE-ISSUED: February 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pieczenik; George	New York	NY	10023	N/A

US-CL-CURRENT: 435/69.1; 435/320.1, 435/69.3, 435/DIG.17, 435/DIG.23, 435/DIG.35, 435/DIG.37, 435/DIG.47, 530/327, 530/328, 530/329, 530/330, 530/387.9, 536/23.1

ABSTRACT:

In one aspect the invention discloses a matrix comprising a discrete population of random oligopeptides of the same length, the length being selected from about 4 to about 12 L-amino acid residues, the population comprising at least 10% of all amino acid sequences of the selected length; and a heterogeneous population of antibodies comprising antibodies capable of binding to substantially every member of the oligopeptide population.

92 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

☐ Generate Collection

L21: Entry 2 of 2 File: USPT Feb 16, 1999

US-PAT-NO: 5871974
DOCUMENT-IDENTIFIER: US 5871974 A

TITLE: Surface expression libraries of heteromeric receptors

DATE-ISSUED: February 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

US-CL-CURRENT: 435/69.7; 435/252.3, 435/320.1, 435/69.1, 536/23.4

ABSTRACT:

A composition of matter comprising a plurality of procaryotic cells containing diverse combinations of first and second DNA sequences encoding first and second polypeptides which form a heteromeric receptor exhibiting binding activity toward a preselected molecule, those heteromeric receptors being expressed on the surface of filamentous bacteriophage.

32 Claims, 16 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 16

End of Result Set

Generate Collection

L22: Entry 1 of 1 File: USPT Sep 21, 1999

US-PAT-NO: 5955358
DOCUMENT-IDENTIFIER: US 5955358 A

TITLE: Optimization of binding proteins

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Huse; William D.	Del Mar	CA	N/A	N/A

US-CL-CURRENT: 435/328; 435/6, 435/70.21, 435/91.5, 436/548, 530/387.3, 530/388.1

ABSTRACT:

The invention relates to methods for manipulating nucleic acids so as to optimize the binding characteristics of an encoded binding protein by providing two or more nucleic acids encoding binding proteins having at least one set of splicing sites, the set of splicing sites flanking opposite ends of one or more encoded binding domains; mixing the nucleic acids to produce a parent population of mixed nucleic acids encoding binding proteins; and randomly incorporating the binding domains between the nucleic acids through the set of splicing sites to produce a different population of nucleic acids encoding binding proteins wherein at least one binding protein is characterized by substantially different binding characteristics than a member of the parent population.

29 Claims, 1 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 1

End of Result Set

☐ Generate Collection

L23: Entry 5 of 5 File: USPT Sep 28, 1999

US-PAT-NO: 5958672
DOCUMENT-IDENTIFIER: US 5958672 A

TITLE: Protein activity screening of clones having DNA from uncultivated microorganisms

DATE-ISSUED: September 28, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A

US-CL-CURRENT: 435/4; 435/183, 435/69.1, 536/23.1, 536/23.2

ABSTRACT:

Disclosed is a process of screening clones having DNA from an uncultivated microorganism for a specified protein, e.g. enzyme, activity by screening for a specified protein, e.g. enzyme, activity in a library of clones prepared by (i) recovering DNA from a DNA population derived from at least one uncultivated microorganism; and (ii) transforming a host with recovered DNA to produce a library of clones which is screened for the specified protein, e.g. enzyme, activity.

15 Claims, 5 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 5

End of Result Set

☐ Generate Collection

L24: Entry 3 of 3 File: USPT Oct 12, 1999

US-PAT-NO: 5965408
DOCUMENT-IDENTIFIER: US 5965408 A

TITLE: Method of DNA reassembly by interrupting synthesis

DATE-ISSUED: October 12, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A

US-CL-CURRENT: 435/91.1; 435/183, 435/6, 435/91.2, 436/501, 530/350, 536/23.1, 536/24.3, 536/24.33

ABSTRACT:

Disclosed is a process of performing Sexual PCR which includes generating random polynucleotides by interrupting or blocking a synthesis or amplification process to show or halt synthesis or amplification of at least one polynucleotide, optionally amplifying the polynucleotides, and reannealing the polynucleotides to produce random mutant polynucleotides. Also provided are vector and expression vehicles including such mutant polynucleotides, polypeptides expressed by the mutant polynucleotides and a method for producing random mutant polypeptides.

14 Claims, 2 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 6

End of Result Set

Generate Collection

L25: Entry 1 of 1 File: USPT Nov 2, 1999

US-PAT-NO: 5976862
DOCUMENT-IDENTIFIER: US 5976862 A

TITLE: Process for obtaining DNA, RNA, peptides, polypeptides, or proteins, by recombinant DNA technique

DATE-ISSUED: November 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kauffman; Stuart Alan	Santa Fe	NM	N/A	N/A
Ballivet; Marc	Geneva	N/A	N/A	CHX

US-CL-CURRENT: 435/252.3; 435/471, 435/476, 435/6, 435/69.1, 435/71.1, 435/91.1, 435/91.4

ABSTRACT:

The present invention is directed to a process for the production of a peptide, polypeptide, or protein having a predetermined property. In accordance with one embodiment, the process begins by producing by way of synthetic polynucleotide coupling, stochastically generated polynucleotide sequences. A library of expression vectors containing such stochastically generated polynucleotide sequences is formed. Next, host cells containing the vectors are cultured so as to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences. Screening or selection is carried out on such host cells to identify a peptide, polypeptide, or protein produced by the host cells which has the predetermined property. The stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein is then isolated and used to produce the peptide, polypeptide, or protein having the predetermined property.

34 Claims, 0 Drawing figures Exemplary Claim Number: 1

End of Result Set

☐ Generate Collection

L26: Entry 1 of 1 File: USPT Nov 23, 1999

US-PAT-NO: 5989553
DOCUMENT-IDENTIFIER: US 5989553 A

TITLE: Expression library immunization

DATE-ISSUED: November 23, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnston; Stephen A.	Dallas	TX	N/A	N/A
Barry; Michael A.	Carrollton	TX	N/A	N/A
Lai; Wayne C.	Richardson	TX	N/A	N/A

US-CL-CURRENT: 424/190.1; 424/184.1, 424/185.1, 424/188.1, 424/201.1, 424/207.1, 424/208.1, 424/234.1, 424/248.1, 424/263.1, 424/264.1, 435/325, 435/440, 435/455, 435/489, 514/2, 530/403, 530/806, 530/825, 530/826, 530/868

ABSTRACT:

A general method for vaccinating against any pathogen is presented. The method utilizes expression library immunization, where an animal is inoculated with an expression library constructed from fragmented genomic DNA of the pathogen. All potential epitopes of the pathogen's proteins are encoded in its DNA, and genetic immunization is used to directly introduce one or more expression library clones to the immune system, producing an immune response to the encoded protein. Inoculation of expression libraries representing portions of the Mycoplasma pulmonis genome was shown to protect mice from subsequent challenge by this natural pathogen. Protection against Listeria.

6 Claims, 14 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 11

End of Result Set

☐ Generate Collection

L27: Entry 1 of 1 File: USPT Dec 14, 1999

US-PAT-NO: 6001574
DOCUMENT-IDENTIFIER: US 6001574 A

TITLE: Production and use of normalized DNA libraries

DATE-ISSUED: December 14, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A
Mathur; Eric J.	Carlsbad	CA	N/A	N/A

US-CL-CURRENT: 435/6; 435/440, 435/91.2, 536/25.4, 536/25.42

ABSTRACT:

Disclosed is a process for forming a normalized genomic DNA library from an environmental sample by (a) isolating a genomic DNA population from the environmental sample; (b) at least one of (i) amplifying the copy number of the DNA population so isolated and (ii) recovering a fraction of the isolated genomic DNA having a desired characteristic; and (c) normalizing the representation of various DNAs within the genomic DNA population so as to form a normalized library of genomic DNA from the environmental sample. Also disclosed is a normalized genomic DNA library formed from an environmental sample by the process.

14 Claims, 1 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 1

End of Result Set

☐ Generate Collection

L28: Entry 1 of 1 File: USPT Dec 21, 1999

US-PAT-NO: 6004788
DOCUMENT-IDENTIFIER: US 6004788 A

TITLE: Enzyme kits and libraries

DATE-ISSUED: December 21, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A

US-CL-CURRENT: 435/183; 435/189, 435/190, 435/191, 435/193, 435/194, 435/195, 435/212, 435/232, 435/4

ABSTRACT:

Recombinant enzyme libraries and kits where a plurality of enzymes are each characterized by different physical and/or chemical characteristics and classified by common characteristics. The characteristics are determined by screening of recombinant enzymes expressed by a DNA library produced from various microorganisms.

2 Claims, 4 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 4

End of Result Set

☐ Generate Collection

L29: Entry 1 of 1 File: USPT Feb 29, 2000

US-PAT-NO: 6030779
DOCUMENT-IDENTIFIER: US 6030779 A

TITLE: Screening for novel bioactivities

DATE-ISSUED: February 29, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A

US-CL-CURRENT: 435/6; 435/91.2

ABSTRACT:

Disclosed is a process for identifying clones having a specified enzyme activity by screening for the specified enzyme activity in a library of clones prepared by (i) selectively isolating target nucleic acid from nucleic acid derived from at least one microorganism, by use of at least one polynucleotide probe comprising at least a portion of a nucleic acid sequence encoding an enzyme having the specified enzyme activity; and (ii) transforming a host with isolated target nucleic acid to produce a library of clones which are screened for the specified enzyme activity.

38 Claims, 3 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 1

Generate Collection

L30: Entry 1 of 3 File: USPT Apr 25, 2000

US-PAT-NO: 6054267
DOCUMENT-IDENTIFIER: US 6054267 A

TITLE: Method for screening for enzyme activity

DATE-ISSUED: April 25, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinias	CA	N/A	N/A

US-CL-CURRENT: 435/6; 435/69.1

ABSTRACT:

Disclosed is a process for identifying clones having a specified enzyme activity by screening for the specified enzyme activity in a library of clones prepared by (i) selectively isolating target DNA from DNA derived from at least one microorganism, by use of at least one probe DNA comprising at least a portion of a DNA sequence encoding an enzyme having the specified enzyme activity; and (ii) transforming a host with isolated target DNA to produce a library of clones which are screened for the specified enzyme activity.

24 Claims, 2 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 1

End of Result Set

☐ Generate Collection

L31: Entry 1 of 1 File: USPT May 2, 2000

US-PAT-NO: 6057103
DOCUMENT-IDENTIFIER: US 6057103 A

TITLE: Screening for novel bioactivities

DATE-ISSUED: May 2, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Short; Jay M.	Encinitas	CA	N/A	N/A

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 436/501, 536/23.1, 536/24.3, 536/24.31, 536/24.32, 536/24.33, 536/25.4

ABSTRACT:

Disclosed is a process for identifying clones having a specified activity of interest, which process comprises (i) generating one or more expression libraries derived from nucleic acid directly isolated from the environment; and (ii) screening said libraries utilizing an assay system. More particularly, this is a process for identifying clones having a specified activity of interest by (i) generating one or more expression libraries derived from nucleic acid directly or indirectly isolated from the environment; (ii) exposing said libraries to a particular substrate or substrates of interest; and (iii) screening said exposed libraries utilizing a fluorescence activated cell sorter to identify clones which react with the substrate or substrates. Also provided is a process for identifying clones having a specified activity of interest by (i) generating one or more expression libraries derived from nucleic acid directly or indirectly isolated from the environment; and (ii) screening said exposed libraries utilizing an assay requiring a binding event or the covalent modification of a target, and a fluorescence activated cell sorter to identify positive clones.

33 Claims, 10 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 8

End of Result Set

☐ Generate Collection

L32: Entry 1 of 1 File: USPT Aug 1, 2000

US-PAT-NO: 6096548
DOCUMENT-IDENTIFIER: US 6096548 A

TITLE: Method for directing evolution of a virus

DATE-ISSUED: August 1, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Stemmer; Willem P. C.	Los Gatos	CA	N/A	N/A

US-CL-CURRENT: 435/440; 435/91.2

ABSTRACT:

The invention provides a number of strategies for transferring and/or evolving gene(s) associated with cellular DNA uptake so that they confer or enhance DNA-uptake capacity of a recipient cell. Evolution is achieved by recursive cycles of recombination and screening/selection. One such strategy entails evolving genes that confer competence in one species to confer either greater competence in that species, or comparable or greater competence in a second species. Another strategy entails evolving genes for use as components of cloning vector to confer enhanced uptake of the vector. Other strategies entail evolving viral receptors, viruses, and genes that mediate conjugal transfer.

14 Claims, 9 Drawing figures Exemplary Claim Number: 1
Number of Drawing Sheets: 9